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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,480	04/17/2007	Charles Reay Mackay	RICE-050	3065

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,480	MACKAY, CHARLES REAY	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22,27,28,30-35 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22,27,28,30-35 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-8-11 has been entered.

Claims 6-9, 11-13, 21, 23-26, 29, 36-39 and 41 have been canceled. Claims 1-5, 10, 1-20, 22, 27, 28, 30-35 and 40 remain pending.

Applicant's arguments filed 2-8-11 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Please do not use bold face type when amending claims.

Specification

The title of the invention has been changed to more closely reflect the fact that the claims are limited to a transgenic mouse.

Claim Rejections - 35 USC § 101

The rejection of claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. 101 because the claimed invention lacks patentable utility was previously withdrawn because agonists and antagonists of C5aR were known in the art as being

used for therapy (pg 2, lines 9-21). One such known antagonist to C5aR known to treat disease was 3D53 (Monk of record, 2007; pg 436, paragraph bridging col. 1-2; col. 2, 1st full paragraph). Monk (2007) summarized treatment using 3D53 on pg 437 (Table 2), many of which were known prior to 12-24-03 (see "References" column of Table 2, which was many references published in 2003 or before). In addition, pg 62, lines 20-35, discuss a method of screening drugs using homozygous human C5aR knockin mice.

Claim Rejections - 35 USC § 112

New matter

The rejection of claims 28, 30-35, 40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of pg 6, lines 8-10; pg 7, line 32, through pg 8, line 2.

Enablement

The rejection of claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn.

In particular, the rejection regarding making the knockin mouse has been withdrawn in view of pg 52, lines 28-35, which states: “The targeting vector used to generate the knock-in mice includes regions homologous to approximately 3kb genomic DNA either side of exon 3 (i.e. from about nucleotides 7377-15045 as shown in SEQ ID NO: 1). In particular, the targeting vector comprised the region from about nucleotides 7377-15045 of SEQ ID NO: 1 except that nucleotides 10726-11778 were replaced by

nucleotides 28 to 1077 of SEQ ID NO:2. This means that following integration, the endogenous mouse exons 1 and 2 remain in the transgenic mammal but exon 3 of the mouse locus has been replaced with a sequence encoding human C5aR."

The rejection regarding using a cre-lox system to make the mouse claimed has been withdrawn in view of applicants' arguments.

The rejection of claim 28 has been withdrawn in view of applicants' arguments. The mice claimed can be used to screen compounds already known to target C5aR for in vivo pharmacodynamics and pharmacokinetics.

The rejection of claims 1-5, 10, 12, 14-20, 22, 27, 28, 30-35 and 40 regarding mice expressing human or humanized C5aR while still expressing their endogenous C5aR gene has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 103

Claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (Thrombosis and Haemostasis, 1999, Vol. 82, No. 2, pg 865-869), Roebroek (Methods in Molecular Biology, 2003, Vol. 209, 187-200), Homanics (2002, Methods in Alcohol related neuroscience research, Editor, Liu, Yuan, pg 31-61), Lester (Current Opin. Drug Discovery and Development, 2003, Vol. 6, No. 5, pg 633-639), Champtiaux (Current Drug Targets-CNS & Neurological Disorders, 2002, Vol. 1, pg 319-330), Girardi (J. Clin. Invest., Dec. 2003, Vol. 112, No. 11, pg 1644-1654) in view of Burmer (WO 02/61087-A2) and Cain (Biochemical Pharm., 2001, Vol. 61, No. 12, pg 1571-1579) and supported by Drago (Cellular and molecular life sciences, July

2003, Vol. 60, pg 1267-1280), Gu (Developmental Cell, July 2003, Vol. 5, pg 45-57), Belmont (WO 2002/059263), and Kane (WO 2003/027252).

Sato taught a knock-in mouse had an endogenous gene replaced with an exogenous gene or a mutant form of the endogenous gene (pg 866, col. 1, Gene Knock-in). Roebroek taught various strategies for making knockin mice and provided numerous references prior to applicants effective filing date that describe disrupting an endogenous mouse gene and replacing it with the human homologous cDNA (pg 188, 2.2; pg 190-191, 3.1) where the human receptor encoded by the transgene binds the mouse ligand and functions in vivo. One example of a receptor mouse known at the time of filing was Homanics who taught disrupting a mouse receptor gene and replaced with homologous human receptor cDNA. Other examples of receptor knockin mice are described by Lester and Champtiaux. Cells were isolated from the mice, and compounds were administered to the mice for pharmacokinetic evaluation. Sato, Roebroek, Homanics, Lester, Champtiaux did not disrupt the mouse C5aR gene and replace it with human C5aR cDNA.

However, knocking out the mouse C5aR gene in a mouse was known in the art at the time of filing as described by Girardi. Furthermore, human C5aR cDNA was known in the art at the time of filing as described by Burmer (SEQ ID NO: 79). In addition, Cain taught mutated human C5aR that functioned in rat cells that “resemble mouse at these positions” (pg 1573, col. 2, section 3.2).

Thus it would have been obvious to those of ordinary skill in the art at the time the invention was made to make a humanized receptor knockin mouse as was well

known in the art at the time of filing using the human C5aR cDNA of Burmer or the mutated human C5aR of Cain. Those of ordinary skill in the art at the time the invention was made would have been motivated to replace the mouse C5aR gene with human C5aR cDNA to test the functional redundancy of the gene, i.e. to test whether or not the exogenous gene can replace the function of the endogenous gene.

In addition, knockin mice having a humanized receptor were known in the art to bind the mouse ligand as exemplified by Drago (Cellular and molecular life sciences, July 2003, Vol. 60, pg 1267-1280; a leucine-to-serine point mutation in a critical residue within the second transmembrane domain of the α4 nAChR subunit (L9'S knockin); pg 1274, col. 1, 2nd partial paragraph), Gu (Developmental Cell, July 2003, Vol. 5, pg 45-57), Belmont (WO 2002/059263) and Kane (WO 2003/027252). Finally, the claims encompass mice having a point mutation in the mouse receptor that is found in the human receptor (a humanized receptor as claimed); the claims are not limited to a mouse expressing the entire human C5aR in the absence of the mouse C5aR. Thus, those of ordinary skill in the art at the time of filing would have had a reasonable expectation of obtaining a mouse expressing a human C5aR or humanized C5aR that bound mouse C5a that effects signaling as claimed.

Response to arguments

Applicants' discussion on pg 20-21 of the response filed 2-8-11 is noted; however, the argument cannot be discerned. It is also noted that the discussion refers to a "human C5aR knock-in mouse" which appear to be the mouse most closely relating to the mouse of claim 1, and a transgenic human C5aR mouse which does not

necessarily have a disruption of the endogenous C5aR coding sequences as now claimed. On pg 21, applicants summarize that arthritis in "transgenic human C5aR mice is due to binding of the endogenous mouse C5a ligand"; however, this is not an argument (and does not refer to “knock-in” mice as now required in claim 1 as amended).

Applicants argue Cain is irrelevant to the claimed invention because they were simply investigating why synthetic C5aR antagonist has less affinity for mouse C5aR than for human C5aR. Applicants’ argument is not persuasive. Cain taught mutated human C5aR that were made to “resemble mouse at these positions” functioned in rat cells (pg 1573, col. 2, section 3.2). Therefore, despite the lack of 100% homology of mouse and human C5aR, those of ordinary skill would have known how to make a mutated human C5aR that functioned in murine cells and had a reasonable expectation of mouse C5a binding human C5aR as evidenced by Cain. Furthermore, the claims encompass using any “humanized C5aR” which encompasses any mutation that makes the mouse C5aR more like human C5aR (including the mutation described by Cain or any single amino acid substitution that make the mouse C5aR more like human C5aR). The claims are not limited to replacing the entire mouse gene with the entire human gene. It is also noted that variation in binding of agonists to mouse and human C5aR fails to indicate mouse C5a will not bind and effect signaling of human C5aR.

The transgenic mice described by applicants did not have a normal phenotype; therefore, it is unclear mouse C5a does bind to and effect proper signaling of the human

C5aR. Accordingly, it is not readily apparent that binding and proper signaling of mouse C5a and human C5aR can be considered the "unexpected results".

Next, Cain taught mutated human C5aR that were made to "resemble mouse at these positions" functioned in rat cells (pg 1573, col. 2, section 3.2). Therefore, despite the lack of 100% homology of mouse and human C5aR, those of ordinary skill would have known how to make a mutated human C5aR that functioned in murine cells and had a reasonable expectation of mouse C5a binding human C5aR as evidenced by Cain.

It is noted that the claims encompass using any "humanized C5aR" which encompasses any mutation that makes the mouse C5aR more like human C5aR (including the mutation described by Cain or any single amino acid substitution that make the mouse C5aR more like human C5aR). The claims are not limited to replacing the entire mouse gene with the entire human gene. The claims are not limited to obtaining binding and proper signaling of mouse C5a and human C5aR, and it is not readily apparent that proper signaling occurs given the abnormal phenotype of the knock-in mice.

It is also noted that applicants' arguments regarding Cain indicate a difference in binding of known agonists to mouse and human C5aR; however, variation in binding of agonists to mouse and human C5aR fails to indicate mouse C5a will not bind and effect signaling of human C5aR.

Applicants argue Drago did not teach humanized receptor bound mouse ligand. Applicants' argument is not persuasive. Pg 1274, col. 1, 2nd partial paragraph, shows a leucine-to-serine point mutation in a critical residue within the second transmembrane domain of the α4 nAChR subunit (L9'S knockin) effects signaling which implies binding of ligand to the receptor. Applicants' citation of Labarca is noted but does not alter the facts disclosed by Drago.

Applicants argue Gu did not teach humanized receptor bound any of the multiple possible mouse ligands. Applicants' argument is not persuasive. Gu taught a 7 amino acid substitution in the receptor (Fig. 1B), which is a humanized receptor. Gu taught the humanized receptor effected signaling which implies binding of at least one of the multiple ligands to the receptor.

Applicants' discussion of the other references on pg 25-27 of the response filed 2-8-11 is noted, but no other arguments have been set forth.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Kedmi, Society for Neurosci. Abstract Viewer and Itinerary Planner, 2003, Vol. 2003, pp Abstract No. 533.12

Wang, Blood, 2002, Vol. 11, Nol. 11, Abstract 2681

Rozmahel (Human Mol. Genetics, 1997, Vol. 6, Nol. 7, pg 1153-1162)

Woodruff (Arthritis and Rheumatism, Sept. 2002, Vol. 46, No. 9, pg 2476-2485).

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday through Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner